

Significance of Non-Invasive Markers as Predictor of Esophageal Varices in Liver Cirrhosis

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ABSTRACT

Introduction: Upper gastro-intestinal endoscopy remains the gold standard for screening for esophageal varices but it has its own limitations. It is an invasive, expensive and uncomfortable procedure and needs clinical expertise. Accordingly, this study was conducted to establish the role of non-invasive markers for prediction of esophageal varices in liver cirrhosis.

Methods: A hospital based descriptive cross-sectional study was carried out in Liver unit of National Academy of Medical Sciences, Bir Hospital, from October 2016 to September 2017. Complete blood count, liver function test, liver ultrasound and upper gastro-intestinal endoscopy were done for all patients to detect esophageal varices and to correlate with different non-invasive markers.

Results: Total 191 patients of liver cirrhosis were studied after exclusion. Platelet count of $92082.00 \pm 43435.83/\text{mm}^3$ and spleen size of 144.21 ± 10.71 mm was found to be good predictors of presence of EV ($P \leq 0.001$). Significant association between Child-Turcotte-Pugh class and presence of varices was observed ($P \leq 0.001$). AST/ALT ratio with cutoff value of 1.415 showed sensitivity of 82.4% and specificity of 36.4%. APRI at a cutoff value of 1.3 showed a sensitivity of 83.2% and specificity of 50%.

Conclusions: Platelet count, spleen size and Child-Turcotte-Pugh class are good predictors of presence of esophageal varices in patients with liver cirrhosis. AST/ALT ratio and APRI score are not good substitutes for upper gastro-intestinal endoscopy.

Keywords: *esophageal varices; liver cirrhosis; non-invasive markers; portal hypertension; upper gastro-intestinal.*

INTRODUCTION

Cirrhosis is characterized by fibrosis and the conversion of normal liver architectures into structurally abnormal nodules.¹ Portal hypertension leads to the formation of esophageal varices (EV) and variceal hemorrhage is one of the most lethal complications of cirrhosis.²

Upper Gastro-intestinal (UGI) endoscopy still remains the gold standard for screening, but not without

limitations. It is invasive, expensive and needs expertise which may be not available in all centers.

Therefore, the present study was undertaken to

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determine the significance of various non-invasive markers like platelet count, spleen size, AST/ALT ratio and APRI score in predicting EV.

METHODS

This hospital based descriptive cross-sectional study was carried out in Liver unit of National Academy of Medical Sciences, Bir Hospital, Nepal from October 2016 to September 2017. Ethical approval was taken from Institutional Review Board (IRB), NAMS and written informed consent was taken from each patient. Consecutive cases attending Liver unit as outdoor basis and or admitted in ward were enrolled in the study who fulfilled the criteria of liver cirrhosis, defined as having at least one clinical sign of hepatocellular failure and one of portal hypertension along with at least three ultrasonography (USG) findings suggestive of cirrhosis of liver.³ The following cases with cirrhosis with portal hypertension were excluded from the study: Patient presenting with variceal bleed or past history of bleeding, patient who had undergone band ligation, patient with hepatocellular carcinoma, cirrhosis with portal vein thrombosis, patient in hepatic encephalopathy grade III or IV and patient refusing for consent.

A detailed history was taken along with general physical examination and examination of the abdomen was done. Complete blood count was done by automated cell counter, Sysmex 550. Peripheral blood smear was done to rule any other hematological cause of thrombocytopenia. Liver function test was done by Erba XL 300, automated analyzer. Prothrombin time and international normalized ratio was also calculated. All the blood investigations were verified by pathologist before dispatching. All patients underwent 2D ultrasound study of hepatobiliary system for liver architecture and nodularity, spleen bipolar diameter, presence of ascites by Sonosite Micromax doppler ultrasound. UGI endoscopy for all patients was done after overnight fasting with flexible gastroduodenal endoscope (FUJINON). EV were classified as small if varices flattened with insufflations or minimally protrude into the esophageal lumen and large if they protruded into the esophageal lumen and touch each other (presence of confluence), or that filled at least 50% of the esophageal lumen.⁴ Child-Turcotte-Pugh (CTP) score was calculated to assess the severity of liver disease.⁵ APRI score, an index ratio of aspartate aminotransferase (AST) and platelets counts was calculated as formulated by Wai CT et al.⁶

Aspartate aminotransferase (AST)/upper normal limit of AST x 100

$$\frac{\text{Platelet counts (10}^{9/L})}{\text{Upper normal limit of platelet count}}$$

A cut off value of 1.3 proposed by Castera et al, was used, value lower than this was supposed not to have

EV.⁷

Sample size was calculated by following formula:

$$n = 4 \left[\frac{Z_{\alpha} + Z_{\beta}}{\ln \frac{(1+\rho)}{(1-\rho)}} \right]^2 + 3$$

Assuming small effect size of 0.2 at 5% significance level with $z_{\alpha} = 1.96$, with 80% power with $z_{\beta} = 0.84$, using formula minimum sample size was 191. Data collected in structured proforma were entered in Microsoft Excel 2007 and statistical analysis was done with SPSS 20 software. Chi-Square test was used for comparisons between categorical variables. Receiver Operating Characteristic (ROC) curves for AST/ALT ratio was applied for prediction of EV. Values were expressed as mean \pm SD, a 95% confidence interval was taken and P values of <0.05 was considered to be statistically significant.

RESULTS

Three hundred and fifty patients were enrolled during the study period, 159 were excluded and finally 191 patients were studied. During UGI endoscopy, EV was present in 125 patients (65.4%). Significant relation between CTP class and presence of varices was observed (Chi sq. test statistic = 84.808; $P \leq 0.001$). Varices were present in majority of cases with CTP class C (Table 1).

Table 1. Relation between CTP classes and EV.

CTP Class	NEV	EV	Total	Chi-Square	P value
A	4	6	10	84.808	<0.001
B	40	57	97		
C	22	62	84		
Total	66	125	191		

NEV= No Esophageal varices, EV= Esophageal varices

Platelet count and spleen diameter was calculated as a non-invasive tool for predictor of EV. Significant relation between platelet count and spleen size with presence of EV was observed (Table 2).

Table 2. Relationship between Platelet count and Spleen size with EV.

Variable	Mean	SD	EV	P value
Platelet (n/mm ³)	92082.00	43435.83	Yes	<0.001
	234610.00	223953.00	No	
Spleen size (mm)	144.21	10.71	Yes	<0.001
	127.09	21.24	No	

EV= Esophageal varices, SD= Standard deviation

Receiver operating characteristic (ROC) curve of AST/ALT when plotted as a predictor of EV with cutoff value of 1.415 showed sensitivity of 82.4% and specificity of 36.4% (Table 3, Figure 1).

Table 3. ROC curve for sensitivity and specificity of AST/ALT ratio for prediction of EV.

Area Under Curve				
Area	Std. Error	P	Asymptotic 95% Confidence Interval	
			Lower	Upper
0.586	0.045	0.051	0.498	0.674

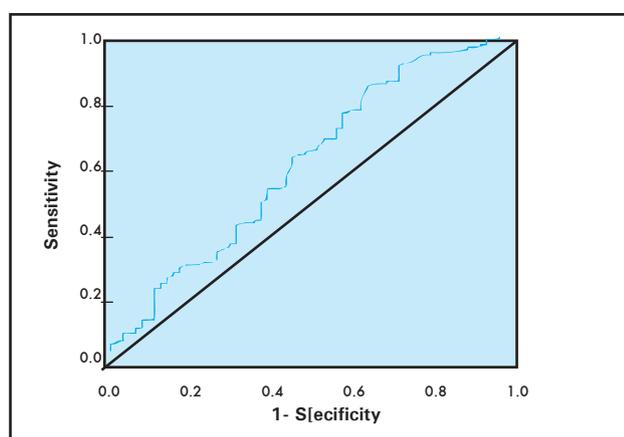


Figure 1. ROC curve for sensitivity and specificity of AST/ALT ratio for prediction of EV.

Correlation between APRI score at a cutoff value of 1.3 and presence of EV (Table 4).

Table 4. Correlation between APRI score and EV.

APRI	EV		Total	Sensitivity	Specificity
	Yes	No			
≥ 1.3	104	33	137	83.2%	50%
< 1.3	21	33	54		
Total	125	66	191		

EV= Esophageal varices

DISCUSSION

Portal hypertension which usually develops as a consequence of cirrhosis is a hyper dynamic state associated with complications like ascites, hepatic

encephalopathy and gastro-esophageal varices. Varices usually develop in cirrhosis when portal pressure, measured as hepatic venous pressure gradient (HVPG) increases up to 10-12 mm Hg.¹ Once varices develop, rate of enlargement from small to large is at a rate of 5-12% per year and bleed at a rate of 5-15% per year.⁸ Early diagnosis of varices before the first bleed is essential because the risk of variceal hemorrhage can be reduced by 50% to about 15% for large esophageal varices if primary prophylaxis initiated timely.⁹ UGI endoscopy remains the gold standard for screening, but this test is not without its own limitations. To overcome this problem some non-invasive parameters have been developed like platelet count, spleen size, CTP class, AST/ALT ratio, APRI score which are simple, quick, reproducible, and cost effective too.

In this study, significant association between CTP class and EV was found. Majority of patients with EV were in CTP class C (P≤0.001). GarciaTsao et al, also reported EV are more common in CTP class C (85%) as compared to class A (40%).¹ This is in tune with our study. CTP class reflected severity of liver disease as higher the score more the disease severity and thus more the incidence of EV.

The mean platelet count of cases with EV was 92082.00±43435.83/mm³ and no EV group was 234610.00±223953.00/mm³ (P≤0.001). Low platelet count (88,000/mm³) as an independent predictor of EV was also reported by Chalasani et al.¹⁰ Thomopoulos et al, observed platelet count of < 118,000/mm³ as a predictor for presence of EV with sensitivity of 95% and specificity of 73%.¹¹ Low platelet count associated with EV was related to hypersplenism developed in liver cirrhosis with progressive rise in portal pressure with due course of time.

The present study showed that average spleen size in patients without EV was 127.09±21.24 mm and with varices was 144.21±10.71 mm (P≤0.001). Splenomegaly (> 135 mm) as a predictor of EV was also reported by Thomopoulos et al.¹¹ In the study by Agha et al, the mean spleen diameter of EV group was 147 mm and no EV group was 109 mm.¹² Splenomegaly in cirrhosis is likely the result of vascular disturbance that are mainly related to portal hypertension.

AST/ALT ratio as a predictor of EV was studied by various studies. In our study AST/ALT ration with cutoff value of 1.415 showed sensitivity of 82.4% and specificity of 36.4% and ROC of 0.586. Nyblom et al, reported higher AST/ALT ratio (1.8 versus 1.0, P≤0.0001) was associated with presence of EV.¹³ Treprasertsuk et al, found an AST/ALT ratio > 1.12 to be significantly associated with the presence of varices a sensitivity of 47.8%, specificity of 87% and an

AUROC of 0.69.¹⁴ Castera et al, using a cut-off of ≥ 1.0 demonstrated a sensitivity of 68%, specificity of 89% with an AUROC 0.83 for predicting the presence of EV.⁷ Different cutoffs for the AST/ALT ratio in different studies may not be confidently predicting the presence of EV in clinical practice to avoid screening all cirrhotic patients with endoscopy.

In our study, APRI at a cutoff value of 1.3 showed a sensitivity of 83.2% and specificity of 50% for predicting EV. Mattos et al, demonstrated a sensitivity of 64% and specificity of 72.7% in predicting EV with similar cutoff value.¹⁵ Stefanescu et al, with a cutoff value of 1.4 demonstrate sensitivity of 66.24% and specificity of 44.59%.¹⁶ Comparing to our study, other studies also could not significantly correlate APRI to presence of EV. APRI with cutoff value of 1.3 as proposed by Castera et al, was based on patients with hepatitis C infection, majority of them were in CTP class of A only.⁷ But majority of patients in our study were in

class CTP B and C which could justify different results.

Our study had few limitations. Portal hypertension which is correctly reflected by measurement of portal pressure as hepatic venous pressure gradient (HVPG) was not done in our study. This is a single center study, may need multicenter study to further validate the diagnostic accuracy of these non-invasive markers as predictor of EV.

CONCLUSIONS

We conclude that platelet count, spleen size, CTP class are good predictors of presence of EV and can be recommended as non-invasive tools for screening of EV in liver cirrhosis. AST/ALT ratio without uniform cutoff value and APRI score with marginal sensitivity and specificity were not appropriate substitute for UGI endoscopy.

Conflict of Interest: None.

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